Buprenorphine / Naloxone and Buprenorphine for Opioid Dependence
Criteria for Use for Office-Based Opioid Treatment (OBOT) Settings

August 2014

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives
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The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.

In every clinical situation, except when the patient is pregnant or has a documented intolerance or hypersensitivity to naloxone, the preferred formulation of buprenorphine is the buprenorphine/naloxone combination. Patients who are pregnant should be carefully educated about the benefits and risks of buprenorphine versus methadone during pregnancy and should make an informed choice about which medication to use. If using buprenorphine during pregnancy, it should be the buprenorphine monodrug product and not the buprenorphine/naloxone combination.

Hereinafter, buprenorphine refers to the buprenorphine/naloxone combination or the monodrug product (in the case of pregnancy or naloxone intolerance/hypersensitivity), unless specifically indicated as either formulation.

Patient Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT* receive buprenorphine

☐ Hypersensitivity to buprenorphine (for monodrug or combination product) or to naloxone (for the combination product) or other components of the formulation

Provider Inclusion Criteria

Also see Exceptions to Waiver Requirement and Other Physician Requirements under ***Issues for Consideration****.*

☐ Is a physician who has met all requirements for a waiver specified by the Drug Addiction Treatment Act (DATA) 2000, Substance Abuse and Mental Health Services Administration (SAMHSA) and U.S. Drug Enforcement Agency (DEA).

The waiver allows qualifying physicians to practice medication-assisted opioid addiction therapy with Schedule III, IV, or V narcotic medications specifically approved by the ***Food and Drug Administration (FDA)*** *without the special registration requirements in the Controlled Substances Act for the provision of medication-assisted opioid therapy. Individual physicians are limited to treating 30 patients concurrently under original waivers and 100 patients concurrently under second waivers.*

AND either ONE of the following:

☐ Has experience in addiction medicine or addiction psychiatry

☐ If inexperienced in addiction medicine, will treat initial patients in consultation with an experienced VA provider or a provider in the Physician Clinical Support System mentoring program for buprenorphine (PCSS-B; http://www.pcssb.org/).

Patient Inclusion Criteria

Also see Opioid Agonist Treatment Options and Discontinuation of Methadone under ***Issues for Consideration***

Sublingual buprenorphine is indicated for opioid agonist treatment of opioid dependence / opioid use disorder (diagnosis based on current version of DSM), including medically supervised withdrawal.

Dosage and Administration

Refer to Product Information and other appropriate references such as *TIP 40, Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* .

Contrary to Product Information instructions for Dosage and Administration, unless the patient is pregnant, buprenorphine/naloxone is the preferred formulation for induction rather than buprenorphine monodrug.

Buprenorphine/naloxone sublingual film is considered to be clinically interchangeable with buprenorphine/naloxone sublingual tablets and the formulations may be switched at the same dose. There is potential for greater bioavailability with the film compared to the tablet; therefore, monitor closely for either over- or underdosing depending on the direction of switching formulations.

Issues for Consideration

FDA-approved Indication and Usage

- Buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets and film are indicated for induction and maintenance therapy of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.
- ZUBSOLV sublingual tablets and buprenorphine/naloxone buccal film are indicated for maintenance therapy of opioid dependence following induction with buprenorphine sublingual tablets or buprenorphine/naloxone sublingual tablets and film. Switching from the SUBOXONE-equivalent tablets or film to ZUBSOLV sublingual tablets or buprenorphine/naloxone buccal film will require different dosage strengths to be administered to the patient because of differences in bioavailability. Refer to product information for specific details.

☐ Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to physicians who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

In VA, buprenorphine sublingual tablets and buprenorphine/naloxone sublingual tablets and film and buccal film are indicated for withdrawal management or maintenance treatment of opioid dependence and should be used as part of a complete treatment plan including medical management and, when indicated, other counseling and psychosocial support.

Buprenorphine injection (FDA-approved for treatment of moderate to severe pain) is NOT sanctioned under DATA 2000 and not FDA-approved for treatment of opioid dependence.

Opioid Agonist Treatment Options

- In combination with nondrug therapy, both methadone and sublingual buprenorphine are first-line therapies for opioid dependence (diagnosis in current version of DSM).
- Although methadone may have advantages over buprenorphine in specific cases, the choice of agent largely depends on the availability of treatment programs and the patient's suitability for care in either an Opioid Treatment Program (where the pharmacotherapeutic choices are methadone and sublingual buprenorphine) or Office-based Opioid Treatment (where the only pharmacotherapeutic option is sublingual buprenorphine) (refer to Table 1).
- The selection of the more appropriate and acceptable modality and setting of addiction treatment should be made as a shared decision between the clinician and the patient, in keeping with existing guidelines.

Table 1 Patient Suitability for Office-based Opioid Treatment Versus Opioid Treatment Program

Criteria*	Office-based Opioid Treatment (OBOT)	Opioid Agonist Treatment Program (OATP)
Can an office-based setting provide needed resources for the patient	Yes	No
Patient's psychosocial supports	Good	Poor
Co-occurring psychiatric disorders	Stable	Unstable (e.g., chronically suicidal)
Dependence on CNS depressants (e.g., alcohol, benzodiazepines)	No	Yes
Previous failed treatment attempts, especially with opioid agonists	None / Few	Many
Response to sublingual buprenorphine in the past	Good	Poor
Expected to be reasonably compliant in treatment	Yes	No
Co-occurring serious pain syndromes (especially those requiring opioids)	No	Yes

Source: VA/DoD Clinical Practice Guideline on Substance Use Disorders (2009) available at http://www.healthquality.va.gov.

* A considerable amount of medical decision-making is required to determine the best setting for each individual patient. If the setting chosen initially is not appropriate, the patient can be switched to the alternative setting with appropriate monitoring.

Monitoring

☐ Patients must be closely supervised and monitored for several hours after administration of each induction dose.

☐ All outpatients should be seen at least weekly for the first two weeks of buprenorphine treatment.

☐ After two weeks, the frequency of visits will be determined by the patient's progress in treatment. However, at a minimum, patients should be seen at least monthly for three months.

☐ Buprenorphine administered as transdermal patches 40 mcg/h (0.96 mg/d) for pain management has been shown to prolong the mean QTc interval on electrocardiogram by a maximum of 9.2 msec (90% CI: 5.2-13.3) (see Product Information for BUTRANS). At this time there are no recommendations for electrocardiographic monitoring for sublingual buprenorphine. Consider the potential for QTc prolongation in patients with hypokalemia or clinically unstable cardiac disease, including:

unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Consider avoiding the use of sublingual buprenorphine in patients with a history of Long QT Syndrome or an immediate family member with this condition, or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide).

☐ Drug Interactions

- *CYP 3A4 inhibitors or inducers:* If CYP 3A4 inhibitors or inducers are co-administered with buprenorphine, patients should be closely monitored and dosage adjusted if necessary. Increased plasma concentrations of buprenorphine have been observed when it was co-administered with the potent CYP 3A4 inhibitor, ketoconazole. Dose reduction may be indicated if buprenorphine is given with CYP 3A4 inhibitors such as azole antifungal agents (e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), HIV protease inhibitors (e.g., ritonavir, indinavir, and saquinavir), the antidepressant, nefazodone, or grapefruit juice. The interaction between buprenorphine and CYP 3A4 inducers (e.g., phenobarbital, carbamazepine, phenytoin, and rifampicin) has not been studied.
- *CNS depressants:* Patients who receive buprenorphine with other central nervous system (CNS) depressants (e.g., other opioid analgesics, general anesthetics, benzodiazepines, phenothiazines, other tranquilizers, sedative-hypnotics, or alcohol) may experience increased CNS depression. Consider reducing the dose of one or both agents if the two agents are co-administered. Buprenorphine tablets, taken orally or sublingually or by injection, have been implicated in fatal drug abuse-related overdoses, particularly when used with benzodiazepines.

Discontinuation of Methadone

- The use of buprenorphine/naloxone for discontinuation of methadone maintenance therapy may be considered on a case-by-case basis

Exceptions to Waiver Requirement (Training on Buprenorphine Therapy is Encouraged)

- *Physicians who order buprenorphine in Opioid Treatment Programs (OTPs)*
- *Physicians who administer or dispense buprenorphine therapy to inpatients or patients in Residential Rehabilitation Treatment Programs (RRTPs) who were admitted for reasons other than treatment of opioid dependence* (e.g., inpatients with myocardial infarction or RRTP patients with posttraumatic stress disorder). A DATA 2000 waiver is not required for practitioners to administer or dispense buprenorphine (or methadone) to a patient with opioid addiction who is admitted for a primary medical problem other than opioid addiction (21 U.S.C. Section 823 (g)(2) and 21 CFR 1306.07). The practitioner may administer opioid agonist medications (e.g., methadone, buprenorphine) to prevent opioid withdrawal that would complicate the primary medical problem. In this situation, consultation with a qualified physician or addiction specialist should be obtained. If a patient is admitted to a hospital or RRTP primarily for treatment of opioid dependence, then only a DATA-waivered physician can order buprenorphine treatment.
- *72-hour Emergency Use***.** According to the 72-hour rule exception, either methadone or buprenorphine/naloxone (or buprenorphine monodrug for pregnant females or persons with hypersensitivity to naloxone) may be used for the emergency treatment of opioid withdrawal by physicians without special DEA registration (including DATA-2000 waiver). Under the 72-hour rule, methadone or sublingual buprenorphine should only be *administered* (and not prescribed) by physicians, one day's worth at a time, for a maximum 72-hour period that cannot be renewed or extended, and only in emergencies. Physicians should document their rationale and decision-making process for exercising the 72-hour rule. The 72-hour rule should not be used for routine medical management of opioid withdrawal ("detox"). For routine management using sublingual buprenorphine outside of an Opioid Treatment Program, waivered physicians are expected to cross-cover for other waivered physicians and to use remote prescribing if possible. Waivered physicians should plan discharge orders accordingly to cover patients on weekends and holidays.

Other Provider-related Guidance

- Although physicians are not required to write a valid waiver identification number on each prescription in the VA, facilities must set up a process to verify that providers are authorized to prescribe buprenorphine for treatment of opioid dependence or to restrict buprenorphine prescribing to only authorized physicians.
- Physicians should be able to refer patients to appropriate ancillary recovery-oriented services in a timely fashion.
- Nonphysicians are prohibited from prescribing buprenorphine. Nonphysicians and nonwaivered physicians may manage patients that have had buprenorphine prescriptions written by waivered physicians.
- It is the physician's responsibility to make sure the necessary resources (such as referrals for ancillary treatment, cross-coverage by a qualified physician, urine drug screening, and secure medication storage) are in place before prescribing buprenorphine. The physician may delegate these responsibilities to other staff members but remains responsible for assuring that appropriate clinical care is delivered.
- Similarly, *before* converting a stable patient from methadone to buprenorphine, the physician should make sure a qualified physician is available to accept the patient upon the patient's transition from an Opioid Treatment Program.

Uses Not Supported by Current Evidence

- Off-label use solely for pain management
- Use of sublingual buprenorphine primarily for analgesia in patients for whom buprenorphine was originally started for treatment of opioid dependence (diagnosis in current version of DSM)

Pregnancy Category C. Use during pregnancy only if the potential benefits outweigh the potential risks.

Quantity Prescribed and Refills

Prescriptions for buprenorphine

- Can be prescribed with refills like other Schedule III drugs; however, patients with opioid dependence should be monitored frequently at reasonable intervals based upon the individual circumstances of the patient.
- Should be of sufficient quantity to last only until the next scheduled appointment with the physician.
- Should have no refills until a stable dosage is achieved and urine or other toxicologic test results are repeatedly negative for drugs that may compromise recovery
- May be considered for refills in patients who are stable and have repeated negative toxicologic tests for drugs that may compromise recovery

Discontinuation Criteria

1) *Discontinuation as a goal of therapy*. While many patients may require long-term maintenance therapy, after a period of social, medical, psychiatric, and substance abstinence stability, clinicians and patients may consider a monitored taper of buprenorphine. Individual response to therapy should determine when to attempt stopping opioid substitution therapy.
2) *Discontinuation for other reasons*. Discontinuation of buprenorphine therapy should be considered if the patient:
   - ☐ Repeatedly misuses, abuses, or diverts buprenorphine or other controlled prescription medications OR
   - ☐ Is noncompliant with clinically indicated supportive care or other ancillary services related to therapy for opioid dependence (diagnosis in current version of DSM) OR
   - ☐ Does not experience suppression of physiologic signs and symptoms of withdrawal with buprenorphine 32 mg daily *after the induction phase.* In this situation, buprenorphine should be stopped, the treatment plan re-evaluated (e.g., for appropriateness of methadone treatment or injectable naltrexone), and a more intensive level of care considered. Inadequate response during the *induction* phase and failure to obtain negative urine drug screens or abstinence should not be used as criteria for discontinuation of buprenorphine.

Updated Sep 2014. Originally prepared and revised: April 2013.
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